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NON-CLINICAL REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

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Applicant: Bioverativ USA. Inc and Sanofi
Review Division: Division of Diabetes, Lipid Disorders and
Obesity
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1 Executive Summary

1.1 Introduction

Bioverativ USA, Inc. seeks to market sutimlimab (proposed proprietary name, Enjaymo), a monoclonal antibody inhibitor of the classical complement pathway, for the treatment of hemolysis in adult patients with cold agglutinin disease (CAD). Sutimlimab was granted orphan and breakthrough therapy designations and the associated Biologics License Application (BLA 761164) was granted priority review.

1.2 Brief Discussion of Nonclinical Findings

Hemolysis in CAD occurs due to an antigen-antibody complex on erythrocytes that activates the classical complement pathway resulting in destruction of erythrocytes. Sutimlimab is a humanized mouse monoclonal immunoglobulin G4 (IgG4) antibody that inhibits classical complement-mediated hemolysis by binding with high affinity (0.26 nM) and inhibiting ($IC_{50} = 1$ nM) the human C1s component of the classical complement pathway. Pharmacological proof-of-concept was confirmed in-vitro, where sutimlimab bound C1s and inhibited the classical complement pathway in serum and plasma samples of hemolytic patients, including those with cold agglutinin disease. Available nonclinical evidence suggests that sutimlimab is specific to the classical complement pathway and does not inhibit the lectin or alternative pathways. Thus, sutimlimab may spare some complement-mediated immune surveillance.

The cynomolgus monkey was the only nonclinical species demonstrated to be pharmacologically relevant, and the nonclinical program was conducted only in that species. Sutimlimab binds cynomolgus monkey and human C1s with comparable affinity (EC_{50} , 0.13 nM and 0.15 nM, respectively) and inhibits classical complement-mediated hemolysis in 20% serum from monkeys and humans with similar potencies (IC_{50} , 4.1 and 5.1 μ g/mL, respectively).

A 26-week toxicity study was conducted in cynomolgus monkeys intravenously administered sutimlimab at 60 and 180 mg/kg/week. Chronic administration of sutimlimab in monkeys led to nearly complete inhibition of classical complement activity (up to 98% reduced activity) at both dose levels. Although the degree of complement inhibition was not dose-dependent, the duration of inhibition was prolonged at 180 mg/kg/week compared to 60 mg/kg/week. This observation is consistent with other monoclonal antibody treatments, where saturation of target is achieved at lower doses, but the durations of pharmacodynamic effects are extended at higher doses due to prolonged systemic clearance. No sutimlimab-related adverse effects were observed up to the highest dose, which represents 5 times the clinical exposures at the 7.5g clinical dose. The classical complement pathway is an important defense against infections, especially encapsulated bacteria, but no signal for increased infections was observed in nonclinical studies. Safety pharmacology endpoints incorporated into the repeat-dose toxicology study in monkeys did not identify any sutimlimab-related adverse effects on cardiovascular, respiratory or central nervous system endpoints at either dose. Sutimlimab was minimally antigenic in monkeys. Anti-drug antibodies (ADA) developed

in 2/10 animals at 60 mg/kg/week and 1/10 animal at 180 mg/kg/week. However, while sutimlimab clearance was increased in these animals, no adverse impacts on the health of animals (e.g., immune complex deposition) were observed. Sutimlimab exposure was unaffected in most animals. Thus, there was minimal impact of the observed immune responses on the interpretability of the study.

No genotoxicity studies were performed with sutimlimab, as monoclonal antibodies are generally considered devoid of mutagenic or clastogenic risk. The applicant provided a weight-of-evidence-based assessment of the carcinogenic potential of sutimlimab. Given the absence of proliferative lesions observed at either dose tested in the chronic monkey study and the lack of any identified tumorigenic risk based on the mechanism of action and a search of the relevant scientific literature, it is unlikely that sutimlimab possesses significant tumorigenic potential. CDER's Executive Carcinogenicity Assessment Committee concurred with this assessment, and no additional studies of the carcinogenic potential of sutimlimab are warranted at this time.

An enhanced pre- and post-natal developmental (ePPND) toxicity study was conducted in pregnant monkeys with intravenous administration of 60 and 180 mg/kg/week sutimlimab (during organogenesis to parturition) to evaluate the potential for embryo-fetal and pre/post-natal developmental toxicity. There were no adverse effects on reproductive or developmental outcomes at 180 mg/kg/week, which represents 4 times the human exposure at the 7.5 g clinical dose. Sutimlimab caused the anticipated inhibition of classical complement pathway activity in maternal animals throughout the dosing period. Drug exposures in maternal animals remained quantifiable during the dosing period. Drug exposures were below the limit of quantitation in maternal animals when analyzed on post-natal days ≥ 28 . Likewise, classical complement activity returned to baseline by 28 days post-partum. Infants were likely exposed to sutimlimab during the (late) third trimester when FcRn-mediated transplacental transfer of maternal immunoglobulin occurs in monkeys, and the drug was detected in the plasma of infants at post-natal day 28. However, by post-natal day 28, sutimlimab was not quantifiable in infant plasma and no classical complement pathway inhibition was detected. No dedicated fertility assessment was conducted with sutimlimab. However, no effects on reproductive tissues that would indicate the potential for sutimlimab to affect fertility were observed in the 26-week repeat-dose study in cynomolgus monkeys at doses up to 180 mg/kg/week, representing up to 5 times the clinical exposures at the 7.5 g clinical dose.

In conclusion, sutimlimab demonstrated robust and prolonged inhibition of the C1s component of the classical complement pathway in a chronic toxicity study in monkeys administered up to 5 times the clinical exposure at the 7.5 g dose. No significant adverse effects were observed. Sutimlimab is unlikely to possess significant carcinogenic risk, and no additional carcinogenicity assessments are recommended. Sutimlimab did not cause adverse reproductive or developmental outcomes when administered to pregnant monkeys at up to 4 times the clinical exposure at the 7.5g dose.

Safety Margins of Sutimlimab in Monkeys Following Repeated Intravenous Administration

| Study | Species | Sex | NOAEL ^a (mg/kg/week) | Basis of NOAEL | AUC (µg.h/mL) | Exposure Margin [#] | |
|---------------------------------|-------------------|-----|------------------------------------|--|----------------------|------------------------------------|------------------------------------|
| | | | | | | <75 kg Human Dose (6.5 g) | ≥75 kg Human Dose (7.5 g) |
| 26-week IV repeat-dose toxicity | Cynomolgus Monkey | M/F | 180 | No sutimlimab-related adverse effects up to the highest dose | 2060000 ^b | 3X | 5X |
| Enhanced PPND toxicity | Cynomolgus Monkey | F | 180 ^d | No sutimlimab-related adverse effects on reproductive or developmental outcomes up to the highest dose | 1670000 ^c | 3X | 4X |

[#]Projected human AUC at the therapeutic doses for subjects <75 kg (6.5 grams; 636 000 µg*h/mL) or ≥75 kg (7.5 grams; 425 000 µg*h/mL); Values are from a simulation based on clinical study data from studies TNT-009-01 (parts A, B, & C) and TNT-009-02.

^aNOAELs are based on the absence of adverse effects at the highest doses/exposures studied.

^bMean AUC_{0-168 h} at steady state on Day 176.

^cMaternal AUC_{0-168 h} on gestation day 146.

^dRepresents the NOAEL for both maternal toxicity and embryofetal/Infant development

1.3 Recommendations

1.3.1 Approvability

Pharmacology/Toxicology supports approval of sutimlimab for the treatment of hemolysis in adult patients with cold agglutinin disease.

1.3.2 Additional Nonclinical Recommendations

1.3.3 Labeling

The applicant's proposed labeling was in PLLR format. Sections 8 (Pregnancy and Lactation), 12.1 (Mechanism of Action), and 13 (Nonclinical Toxicology) in the applicant's proposed label were reviewed. There were no significant disagreements with the applicant's proposal for sections 8, 12.1 and 13. The applicant's label was edited for clarity and to keep it consistent with the PLLR label language. The established pharmacological class (EPC) was changed to "classical complement inhibitor" to be consistent with the EPC text phrase in the FDA EPC list in use for this class. In Section 8.1, Animal Data, the applicant's reference to (b) (4) was removed as (b) (4) are not relevant for this section. Recommended changes to the applicant's proposed label are tracked, below, and the reviewer suggested label follows the applicant's proposed label.

2 Drug Information

2.1 Drug

CAS Registry Number: 2049079-64-1

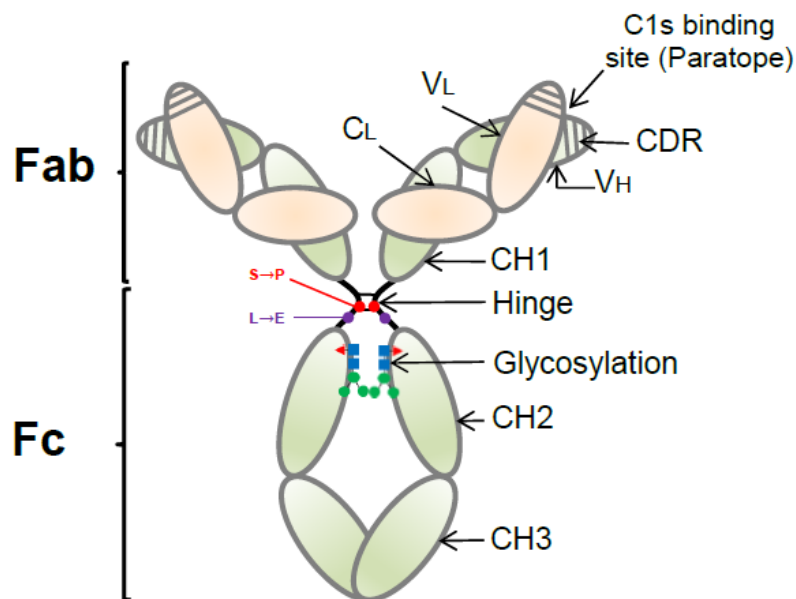
Generic Name: Sutimlimab

Chemical Name: Immunoglobulin G4, anti-(human complement C1s) (humanized mouse monoclonal TNT009 γ 4-chain), disulfide with humanized mouse monoclonal TNT009 k-chain, dimer

Molecular Formula: Sutimlimab, $C_{6436}H_{9938}N_{1700}O_{2013}S_{46}$; Heavy Chain, $C_{2171}H_{3353}N_{573}O_{672}S_{17}$; Light Chain, $C_{1047}H_{1619}N_{277}O_{336}S_6$

Molecular Weight: Sutimlimab, 144,813 Daltons; Each heavy chain, 48,778 Da; Each light chain, 23,655 Da

Structure or Biochemical Description: Sutimlimab is composed of two heterodimers, each containing a heavy and a light chain (Figure 1). Each heavy chain (HC) is composed of 445 amino acids and each light chain (LC) contains 216 amino acids (Figures 2 and 3). The polypeptide is glycosylated at N295. Setmelanotide is engineered to decrease binding to the Fc-gamma receptor owing to a leucine-to-glutamic acid mutation (L248E), which is known to reduce Fc-gamma receptor-mediated effector function.

Figure 1: Schematic of Sutimlimab

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The light chain (shown in light brown) consists of a variable (VL) and a constant (CL) domain while the heavy chain (shown in green) consists of a variable (VH) domain and three constant domains (CH1, CH2 and CH3). Interchain disulfide bonds within the hinge region stabilize the overall antibody structure. The complementarity determining regions (CDR; grey lines) determine specificity for C1s. Additional modifications to BIVV009 include a hinge-stabilizing S→P mutation, and a L→E mutation to reduce Fcγ receptor binding.

Figure excerpted from applicant's report.

Figure 2: Structure of Sutimlimab Heavy Chain**Heavy Chain**

1 EVQLV ESGGG LVKPG GSLRL SCAAS GFTFS NYAMS WVRQA PGKGL EWVAT
 51 ISSGG SHTYY LDSVK GRFTI SRDNS KNTLY LQMNS LRAED TALYY CARLF
 101 TGYAM DYWGQ GTLVT VSSAS TKGPS VFPLA PCSRS TSEST AALGC LVKDY
 151 FPEPV TVSWN SGALT SGVHT FPAVL QSSGL YSLSS VVTVP SSSLG TKTYT
 201 CNVDH KPSNT KVDKR VESKY GPPCP PCPAP EFEGG PSVFL FPPKP KDTLM
 251 ISRTP EVTCV VVDVS QEDPE VQFNW YVDGV EVHNA KTKPR EEQFN STYRV
 301 VSVLT VLHQD WLNGK EYKCK VSNKG LPSSI EKTIS KAKGQ PREPQ VYTLP
 351 PSQEE MTKNQ VSLTC LVKGF YPSDI AVEWE SNGQP ENNYK TTPPV LDSDG
 401 SFFLY SRLTV DKSRW QEGNV FSCSV MHEAL HNHYT QKSLS LSLGK

Note: HC complementarity-determining regions (CDRs) are underlined. The HC glycosylation site (HC N295) is double underlined. Cysteine residues located in the hinge region and forming inter-HC disulfide bonds are shown in bold. Solid lines indicate intra-chain disulfide bonds. Cysteine residue forming interchain disulfide bond is shown in bold and italics.

Figure 3: Structure of Sutimlimab Light Chain**Light Chain**

1 QIVLT QSPAT LSLSP GERAT MSCTA SSSVS SSYLH WYQQK PGKAP KLWY
 56 STSNL ASGVP SRFSG SGSGT DYTTL ISSLQ PEDFA TY^{**YCH**} QYYRL PPITF
 101 GQGK LEIKR TVAAP SVFIF PPSDE QLKSG TASVV CLLNN FYPRE AKVQW
 151 KVDNA LQSGN SQESV TEQDS KDSTY SLSST LTLSK ADYEK HKVYA CEVTH
 201 QGLSS PVTKS FNRGE *C*

Note: LC CDRs are underlined. Solid lines indicate intra-chain disulfide bonds. Cysteine residue forming interchain disulfide bond is shown in bold and italics.

Figures 2 and 3 excerpted from applicant's nonclinical package.

Pharmacologic Class: Classical Complement Inhibitor.

The established pharmacological class (EPC) for sutimlimab is "classical complement inhibitor". This EPC text phrase is based on the mechanism of action of sutimlimab, which is selective inhibition of a classical complement component in the classical pathway. This mechanism of action distinguishes sutimlimab from two approved biologics eculizumab and ravulizumab that share the EPC "complement inhibitor", which is based on inhibition of C5 and prevention of formation of terminal complement complex.

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 128190

Product: BIVV009

Applicant: Bioverativ

Indication: Autoimmune Hemolytic Anemia

2.3 Drug Formulation

Sutimlimab (BIVV009) is formulated for intravenous infusion as a single use vial containing 22 ml of 50 mg/ml sutimlimab (1100 mg sutimlimab/vial) (Table 1). The vial can be diluted with normal saline prior to administration.

Table 1: Composition of Sutimlimab Solution for IV Infusion

| Component | Reference to Standards | Function | Nominal Quantity (per mL) | Nominal Quantity (22 mL/vial) |
|---|------------------------|-------------------|---------------------------|-------------------------------|
| BIVV009 | In-house | Active ingredient | 50 mg | 1100 mg |
| Sodium phosphate monobasic, monohydrate | USP | (b) (4) | 1.13 (b) (4) mg | 24. (b) (4) mg |
| Sodium phosphate dibasic, heptahydrate | USP | (b) (4) | 0.48 mg | 10. mg |
| Sodium chloride | USP, Ph Eur, JP | (b) (4) | 8.18 mg | 180 mg |
| Polysorbate 80 | NF, Ph Eur, JP | (b) (4) | 0.2 mg | 4.4 mg |
| Water for Injection | USP, Ph Eur, JP | (b) (4) | qs to 1 mL | qs to 22 mL |

qs = quantity sufficient

Table excerpted from applicant's nonclinical package

2.4 Comments on Novel Excipients

There are no novel excipients in the drug product, as all excipients in the drug formulation are compendial grade and are present at acceptable levels per the FDA inactive ingredient database.

2.5 Comments on Impurities/Degradants of Concern

Process-Related Impurities:

Residual levels of process-related impurities (host cell proteins, host cell DNA, (b) (4)) were observed in the commercial batches following impurity clearance process by the manufacturer (see Table 2 below).

Table 2: Process-Related Residual Impurities in Drug Substance

(b) (4)



Table excerpted from applicant's package

The applicant proposed permissible daily exposure levels for impurities based on a worst-case scenario at the human dose of 7.5 grams. Acceptability of the proposed levels is addressed, below.

- Host cell protein: The levels present in nonclinical batches (b) (4) covers the levels in the clinical batch (b) (4) as the nonclinical exposure (AUC, NOAEL) in monkeys through intravenous route is 5 times the maximum human exposure.
- Host cell DNA: This impurity was not detected in the nonclinical batch; thus, the safety of this impurity was not qualified in the applicant's 26-week repeat-dose intravenous toxicity study in monkeys. Host cell DNA is present in the clinical batch at the worst-case calculated amount of (b) (4) ng/dose, which is (b) (4) lower than WHO recommended maximum dose of 10 ng/dose ¹.
- (b) (4) Nonclinical studies in which (b) (4) was intravenously injected in mice and monkeys repeatedly did not produce adverse effects at exposures >

¹ WHO Technical Report Series, 1998, Requirements for the Uses of Animal Cells as in vitro Substances for the Production of Biologicals. WHO Expert Committee on Biological Standardization, 47th Report, WHO Technical Report Series 878 Annex 1.

1000-fold compared to worst case scenario of maximum intake of around (b) (4) ng/day in the clinical batch ²³. Furthermore, (b) (4) is present at (b) (4) ppm which is significantly lower than previously an acceptable level of ≤ (b) (4) ppm for (b) (4).

- (b) (4) Expert Panel reviewed the animal and human safety of (b) (4) and found them to be nontoxic even when injected intravenously in animals at > 1000-fold at repeated doses once daily when compared to worst case scenario exposure for the biological ⁴. (b) (4) is water soluble and excreted rapidly in the urine after IV administration in animals.
- (b) (4): The applicant's proposed safety margin was based on the safety of oral use, whereas sutimlimab formulation is intended for IV use. Therefore, the applicant's rationale is of questionable relevance. However, the safety of (b) (4) is supported by its use in another FDA-approved IV formulation, (b) (4). The worst-case scenario at the maximum human dose of 7.5 g sutimlimab would be (b) (4) microgram/day, which is (b) (4) lower than that present in another approved product (b) (4).
- (b) (4) The worst case maximum daily intake based on a maximum human dose of 7.5 grams is (b) (4) ng/day. This exposure is > 1000-fold lower than (b) (4). (b) (4) The extremely low level of (b) (4) in the biological is not a safety concern.

Based on the available nonclinical safety information, described above, the applicant's permissible daily exposure levels appear reasonable and it is unlikely that the residual levels of impurities represent a significant toxicological concern.

Leachables:

An evaluation of potential leachables related to the drug product container closure system was conducted to determine whether they are controlled at acceptable levels (below analytical evaluation threshold, AET) during long-term storage of sutimlimab. The applicant had set the AET of (b) (4) µg/day for leachables, which is (b) (4) µg/mL ((b) (4) ppm) per leachable at the MRHD of 7.5 grams. In an FDA information request dated July 14, 2020, the applicant was asked to calculate AET based on a threshold of toxicological concern (TTC) of (b) (4) µg/day (i.e., for a worst-case for mutagenic compounds) instead of (b) (4) µg/day (i.e., (b) (4)). The applicant, in their

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response dated July 28, 2020, provided a rationale for deriving the AET based on a less-than-lifetime (LTL) exposure paradigm. (b) (4)

For pharmaceuticals with less than lifetime exposure (LTL) as is the case with sutimlimab (once every two weeks), ICH M7 allows for the acceptable cumulative lifetime dose to be uniformly distributed over the total number of exposure days during LTL exposure. The applicant's approach is reasonable.

In the case of sutimlimab, LTL-based risk evaluation indicates a maximum cumulative exposure (e.g., once every two weeks for 70 years in adult patients) to be 1860 days or 5 years. As per ICH M7, Table 2, for exposures >1 year to 10 years, the acceptable daily intake for a mutagen is 10 µg/day, whereas the applicant's proposed AET is lower (b) (4)

Therefore, the applicant's rationale for setting the AET of (b) (4) µg/day for leachables is considered reasonable from a nonclinical perspective.

The applicant's leachables study after 6-month and 12-month storage of sutimlimab under long-term storage conditions (2-8°C, Inverted) yielded (b) (4) leachables above the AET of (b) (4) µg/mL per leachable at the MRHD of 7.5 grams (Table 3). The safety of these leachables were qualified based on published exposure limits or derived from NOAELs (Table 3).

Table 3: Safety Qualification of Leachables from Long-term Stability Testing

| Leachable | Amount Present (ppm) | Amount Present in MRHD of 7.5 g (ppm) | Permitted Daily Exposure (PDE) ppm |
|-----------|----------------------|---------------------------------------|------------------------------------|
| (b) (4) | | | |

| | | | |
|--|--|--|---------|
| | | | (b) (4) |
| | | | |

2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population is adult patients with hemolysis associated with cold agglutinin disease (CAD). The drug is administered as an intravenous infusion at a dosage of 6.5 g for patients 39 kg to < 75 kg body weight, and 7.5 g to patients \geq 75 kg body weight. The dosing regimen is outlined in the table below (Table 4).

Table 4: Dosage and Administration of Sutimlimab

| Body Weight Range (kg) | Initial Dose (Day 0) (g) | Second Dose (Day 7) (g) | Maintenance Dose (every other week, beginning on Day 21) (g) |
|---|--------------------------------|-------------------------------|--|
| greater than or equal to 39 kg to less than 75 kg ¹ | 6.5 | 6.5 | 6.5 |
| 75 kg or more | 7.5 | 7.5 | 7.5 |

(b) (4)

2.7 Regulatory Background

Sutimlimab was granted breakthrough therapy designation for CAD on May 17, 2017 (IND 128190) and the initial rolling BLA submission occurred on July 24, 2019. The applicant submitted nonclinical modules on September 5, 2019.

3 Studies Submitted

3.1 Studies Reviewed

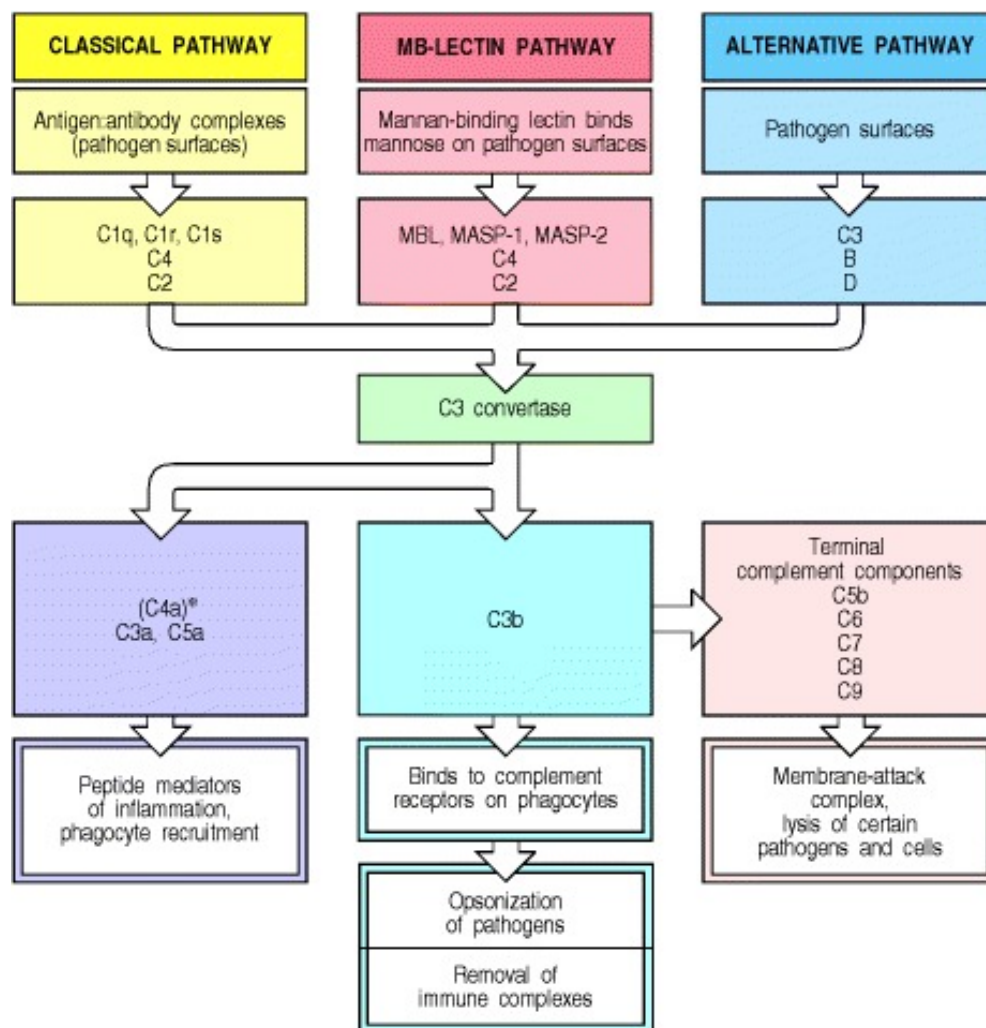
Many studies, including primary pharmacology studies and the chronic 26-week toxicity study in monkeys were reviewed in detail under IND 128190. Therefore, the results of those studies are summarized in this review. The following submissions were not reviewed under the IND, and therefore are described in greater detail in this review:

- T-BV009-01: Enhanced Pre- and Postnatal Developmental Toxicity Study with BIVV009 in Cynomolgus Monkeys
- BIVV009-Carcinogenicity Risk Assessment
- Other Toxicity Studies:
 - TN-1406: Assessment of Potential Cross Reactivity of TNT009 with a Selected Panel of Human Tissues
 - EpiScreen™ Time Course Assay of Fully Humanised Antibody for Immunogenicity Potential

4 Pharmacology

4.1 Primary Pharmacology (Mechanism of Action Related to Proposed Indication)

Sutimlimab (code-named BIVV009, TNT-009) is a humanized mouse immunoglobulin G4 (IgG4) antibody for the treatment of hemolysis in adult patients with cold agglutinin disease (CAD). Hemolysis in CAD is mediated by an antigen-antibody (IgM) complex that activates the classical complement pathway. Sutimlimab binds to and inhibits the complement 1s (C1s) component of the classical complement pathway (Figure 4). C1s is a serine protease which cleaves the first soluble substrate (C4) of the classical complement pathway. Inhibition of C1s thus blocks the cascade of activation of downstream soluble proteases of the classical component pathway and prevents antigen-antibody complex-dependent classical complement-mediated hemolysis. The other two arms of the complement system, namely the alternative and lectin pathways, are not targeted by sutimlimab, thus sparing some level of immune surveillance function of the complement system.

Figure 4: Schematic Illustrating the Three Arms of the Complement System

Charles A Janeway, Jr, Paul Travers, Mark Walport, and Mark J Shlomchik, Editors, 2001, Immunobiology, 5th Edition, New York: Garland Science, accessed June 5, 2020, <https://www.ncbi.nlm.nih.gov/books/NBK10757/>

Sutimlimab (TNT-009) was originally derived from TNT-003, a mouse IgG2a anti-human C1s mAb. Since sutimlimab exhibited C1s binding and inhibitory activities similar to that of TNT-003, the *in vitro* pharmacology of sutimlimab was evaluated using both sutimlimab and TNT003. *In vitro* studies using normal human serum or human complement proteins demonstrated that sutimlimab displayed high affinity binding (2.6×10^{-10} M) and potent and complete inhibitory activity ($IC_{50} = 1.9 \times 10^{-9}$ M) on human C1s of the classical component pathway while not showing any activity on alternate and lectin complement pathways (Table 5).

Table 5: Inhibition of C1s of Classical Pathway but no Inhibition of Alternate or Lectin Pathways

| Antibody | C1s K_D (M) | Wieslab CP IC_{50} (M) | Max CP Inhibition | Wieslab AP | Wieslab LP |
|----------|-----------------------|--------------------------|-------------------|---------------|---------------|
| TNT003 | 5.8×10^{-10} | 1.3×10^{-9} | 100% | No inhibition | No inhibition |
| TNT009 | 2.6×10^{-10} | 1.9×10^{-9} | 100% | No inhibition | No inhibition |

AP = alternative pathway; C1s = complement component 1, s subcomponent; CP = classical pathway (complement system); IC_{50} = half maximal inhibitory concentration; LP = lectin pathway

Table excerpted from applicant's nonclinical package

Species cross-reactivity studies compared the affinity of sutimlimab for human, non-human primate (NHP) and rat C1s using serum on a plate-based binding ELISA assay. Sutimlimab binds to NHP C1s and inhibits antibody mediated complement activation in serum from cynomolgus monkeys with similar potency and activity compared to human serum. Sutimlimab showed weaker binding and no ability to inhibit C1s of rats. Sutimlimab did not bind C1s from mouse.

The cynomolgus monkey was shown to be a pharmacologically relevant species, but no relevant rodent species was identified. Therefore, the sponsor conducted their nonclinical program in the monkey. The binding affinity for C1s (4.1×10^{-10} M and $8.2 \mu\text{g/mL}$ for binding and IC_{50} , respectively) and the pharmacologic activity of sutimlimab in the monkey were similar to those for humans (3.2×10^{-10} M and $5.1 \mu\text{g/mL}$ for binding and IC_{50} , respectively), as seen in Figure 5.

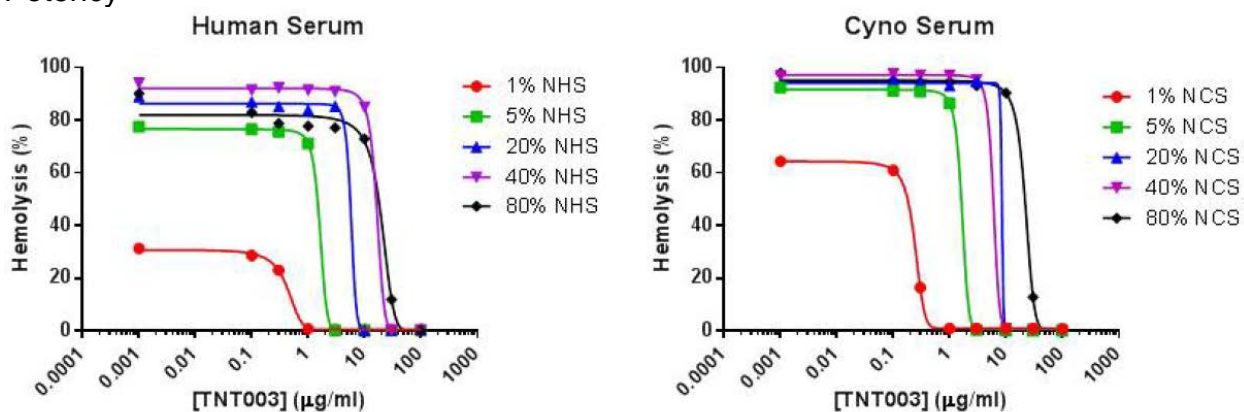
Figure 5: Sutimlimab Inhibits C1s from Human and Monkey Serum with Comparable Potency

Figure excerpted from applicant's nonclinical package

Table 6: Summary of C1s Inhibition by Sutimlimab

| Serum | Human IC ₅₀ (µg/mL) | Cynomolgus IC ₅₀ (µg/mL) |
|-------|--------------------------------|-------------------------------------|
| 1% | 0.38 | 0.18 |
| 5% | 1.2 | 1.3 |
| 20% | 4.1 | 5.1 |
| 40% | 13.0 | 5.1 |
| 80% | 14.7 | 15.6 |

IC₅₀ = half maximal inhibitory concentration

Table excerpted from applicant's nonclinical package

Sutimlimab did not inhibit classical complement-mediated hemolysis in rats, dogs, rabbits, or mini pigs. Sutimlimab is not pharmacologically active in non-primate species (Table 7).

Table 7: Sutimlimab is Pharmacologically Active in Only Humans and NHP

| Species | Binding C1s EC ₅₀ (M) | Hemolysis IC ₅₀ (µg/mL) |
|-------------------|----------------------------------|------------------------------------|
| Human | 4.1×10^{-10} | 8.2 |
| Cynomolgus Monkey | 3.2×10^{-10} | 5.7 |
| Rat | 3.3×10^{-9} | No inhibition |
| Mouse | No binding | Not tested |
| Mini Pig | Not tested | No inhibition* |
| Rabbit | Not tested | No inhibition* |
| Dog | Not tested | No inhibition |

C1s = complement component 1, s subcomponent; EC₅₀ = half maximal effective concentration;

IC₅₀ = half maximal inhibitory concentration

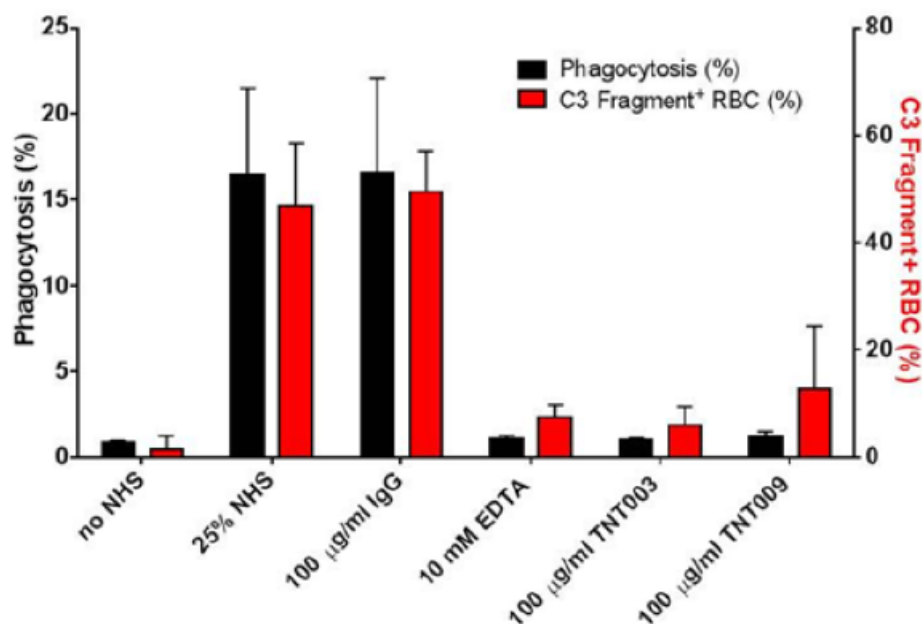
* only tested with TNT003

Table excerpted from applicant's nonclinical package

Ex vivo studies were performed using patient serum and plasma samples specific to complement mediated disorders: CAD, warm autoimmune hemolytic anemia (WAIHA), bullous pemphigoid (BP), and antibody-mediated rejection (AMR)-induced complement activation. Sutimlimab and/or TNT003 (the murine parental mAb of sutimlimab) were shown to inhibit C1s and the classical pathway mediated by auto-antibodies in the patient samples. Using flow cytometry, C3 fragment deposition, a split product of the classical complement pathway that mediates extravascular hemolysis, was measured on the surface of RBCs to assess complement pathway activity. In patients with CAD sutimlimab inhibited CA-mediated C3 fragment deposition in a concentration-dependent manner, with complete inhibition at 10 µg/mL (IC₅₀ = 5.0 ± 1.0 µg/mL).

Cold agglutinin-mediated complement deposition on the surface of RBCs is capable of inducing uptake by phagocytes. To examine sutimlimab's ability to inhibit complement-mediated phagocytosis, RBCs were first sensitized with cold agglutinins and exposed to human serum (source of complement proteins). RBCs were then incubated with Tohoku Hospital Pediatrics-1 (THP-1) monocytic cell line to promote phagocytosis of RBCs. Sutimlimab (100 $\mu\text{g/mL}$) reduced complement deposition and phagocytosis to baseline levels (no serum; 10 mM EDTA), whereas the isotype control mAb did not prevent C3 fragment deposition or phagocytosis (Figure 6).

Figure 6: Sutimlimab Inhibition of Erythrophagocytosis of C3 Fragment-Opsonized



RBCs incubated in CAD plasma were exposed to NHS in the presence of isotype control (IC), 10 mM EDTA, TNT003 or TNT009. C3 fragment deposition was quantified by flow cytometry (C3 Fragment⁺ RBC, red bars). RBCs were then stained with a dye (CFSE), washed, then incubated with THP-1 phagocytes. THP-1 cells staining positive with CFSE were then quantified (phagocytosis %; black bars).

Figure excerpted from applicant's nonclinical package

Of the 40 CAD samples tested, one sample was capable of inducing membrane attack complex (MAC)-mediated lysis of RBCs after exposure to patient plasma and normal human serum. This sample was used to measure the ability of sutimlimab to prevent CA-mediated hemolysis and measure the production (and inhibition) of anaphylatoxins activated by the hemolytic process (C3a, C4a, and C5a), by ELISA. Normal RBCs were sensitized in the patient's plasma and exposed to human serum with various concentrations of sutimlimab. Sutimlimab prevented lysis of cold agglutinin sensitized RBCs. Additionally; sutimlimab inhibited the production of all anaphylatoxins known to contribute to extravascular hemolysis.

4.2 Secondary Pharmacology

As sutimlimab is a humanized IgG4 monoclonal antibody that is selective for C1s with no inhibition of other components (alternate and lectin pathways) off-target potential is considered limited. Thus, secondary pharmacology studies were not conducted for sutimlimab. The applicant performed a tissue cross-reactivity assessment using a select panel of 40 tissues from three human donors to evaluate C1s staining patterns. Consistent with C1s' role as a protein that remains soluble in the absence of any activator of the complement system, no specific staining to relevant cellular structures from healthy, normal tissues was observed.

4.3 Safety Pharmacology

Stand-alone safety pharmacology studies with sutimlimab were not performed, but relevant endpoints were included in the repeat-dose toxicology studies in cynomolgus monkeys (Study # TN-1516). Cardiovascular and respiratory function, including heart rate monitoring, body temperature, oxygen saturation, ECG testing and respirations, were unremarkable at doses up to 180 mg/kg/week for 26 weeks. No effects on central nervous system (CNS) or neurobehavioral endpoints were observed in monkeys at doses up to 180 mg/kg weekly for 26 weeks.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Sutimlimab is a monoclonal antibody that is degraded into smaller peptides and individual amino acids. Thus, classical metabolism studies were unnecessary (consistent with ICH S6). The pharmacokinetics of sutimlimab was evaluated as part of repeat-dose toxicity studies.

6 General Toxicology

Repeat-Dose Toxicity

Study# TN-1516: 26-Week Intravenous Infusion Study in Cynomolgus Monkeys of TNT009 with an 8-Week Recovery Phase

In a GLP-compliant chronic toxicology study, sutimlimab was administered to cynomolgus monkeys by 30-minute intravenous infusion at 2 doses (60 and 180 mg/kg/week) for 26 consecutive weeks with an 8-week treatment-free recovery period.

Toxicology

There were no unscheduled deaths, no distinct target organs of toxicity, and sutimlimab was well tolerated up to the highest dose of 180 mg/kg with no adverse effects.

Pharmacodynamics

Sutimlimab exposure resulted in inhibition of classical complement activity at both doses. The degree of inhibition was not dose-dependent; however, the duration of

inhibition was prolonged at 180 mg/kg/week compared to 60 mg/kg/week. Refer to the Complement Analysis section for greater detail.

Toxicokinetics

Sutimlimab exposure parameters (C_{max} and AUC_{0-48.5}) were similar between males and females. Exposure to sutimlimab increased with increasing dose levels from 60 to 180 mg/kg/dose (Tables 8 and 9). Following the first dose, some accumulation occurred, which is consistent with an approach to steady state with repeated weekly administration. Increases in sutimlimab mean C_{max} and AUC_{0-48.5} were approximately dose proportional on Days 1, 29, 85, and 176.

Table 8. Summary Toxicokinetics of Sutimlimab in Study TN-1516

| Interval | Dose Group | Dose Level (mg/kg/dose) | Sex | C _{max} (ng/mL) | AUC _{0-48.5} (ng·hr/mL) |
|----------|------------|----------------------------|-----|-----------------------------|-------------------------------------|
| Day 1 | 2 | 60 | M | 2130000 | 58000000 |
| | | | F | 1980000 | 33500000 |
| | | | MF | 2050000 | 45800000 |
| | 3 | 180 | M | 7220000 | 183000000 |
| | | | F | 5310000 | 133000000 |
| | | | MF | 6260000 | 158000000 |
| Day 29 | 2 | 60 | M | 2380000 | 54200000 |
| | | | F | 1530000 | 38600000 |
| | | | MF | 1960000 | 46400000 |
| | 3 | 180 | M | 11600000 | 391000000 |
| | | | F | 8100000 | 266000000 |
| | | | MF | 9870000 | 329000000 |
| Day 85 | 2 | 60 | M | 3660000 | 130000000 |
| | | | F | 1550000 | 49700000 |
| | | | MF | 2600000 | 89900000 |
| | 3 | 180 | M | 10800000 | 458000000 |
| | | | F | 10900000 | 380000000 |
| | | | MF | 10800000 | 423000000 |
| Day 176 | 2 | 60 | M | 2320000 | 136000000 |
| | | | F | 2660000 | 79700000 |
| | | | MF | 2490000 | 108000000 |
| | 3 | 180 | M | 14900000 | 229000000 |
| | | | F | 7800000 | 183000000 |
| | | | MF | 11700000 | 206000000 |

F = female; M = male; MF = combined male and female

Table excerpted from applicant's nonclinical package

Table 9. Summary Toxicokinetics of Sutimlimab in Study TN-1516: Day 176

| Dose Group | Dose Level (mg/kg/dose) | Sex | | C _{max} (ng/mL) | DN C _{max} [(ng/mL)/(mg/kg/dose)] | T _{max} (hr) | AUC ₀₋₁ (ng·hr/mL) | AUC _{0-48.5} (ng·hr/mL) | DN AUC _{0-48.5} [(ng·hr/mL)/(mg/kg/dose)] | C _{last} (ng/mL) | T _{last} (hr) | AR C _{max} | AR AUC _{0-48.5} |
|------------|-------------------------|-----|------|--------------------------|--|-----------------------|-------------------------------|----------------------------------|--|---------------------------|------------------------|---------------------|--------------------------|
| 2 | 60 | M | Mean | 2320000 | 38600 | 3.56 | 136000000 | 78400000 | 1310000 | 66000 | 169 | 1.46 | 1.70 |
| | | | SD | 697000 | 11600 | 5.96 | NA | 28700000 | 479000 | NA | NA | 1.11 | 1.14 |
| | | | N | 4 | 4 | 4 | 2 | 4 | 4 | 2 | 2 | 4 | 4 |
| | | F | Mean | 2660000 | 44300 | 25.5 | 79700000 | 67700000 | 1130000 | 80700 | 169 | 1.96 | 2.10 |
| | | | SD | 511000 | 8510 | 26.6 | NA | 20800000 | 347000 | NA | NA | 1.17 | 1.01 |
| | | | N | 4 | 4 | 4 | 2 | 4 | 4 | 2 | 2 | 4 | 4 |
| | | MF | Mean | 2490000 | 41400 | 14.5 | 108000000 | 73000000 | 1220000 | 73300 | 169 | 1.71 | 1.90 |
| | | | SD | 594000 | 9890 | 21.3 | 39100000 | 23900000 | 399000 | 74800 | 0.00 | 1.09 | 1.02 |
| | | | N | 8 | 8 | 8 | 4 | 8 | 8 | 4 | 4 | 8 | 8 |
| 3 | 180 | M | Mean | 14900000 | 82500 | 14.9 | 2290000000 | 575000000 | 3190000 | 777000 | 673 | 3.26 | 3.95 |
| | | | SD | 5490000 | 30500 | 13.1 | NA | 210000000 | 1170000 | NA | NA | 2.00 | 2.03 |
| | | | N | 5 | 5 | 5 | 2 | 5 | 5 | 2 | 2 | 5 | 5 |
| | | F | Mean | 7800000 | 43300 | 0.583 | 1830000000 | 281000000 | 1560000 | 113000 | 841 | 1.75 | 2.32 |
| | | | SD | 394000 | 2190 | 0.00 | NA | 37800000 | 210000 | NA | NA | 0.534 | 0.596 |
| | | | N | 4 | 4 | 4 | 2 | 4 | 4 | 2 | 2 | 4 | 4 |
| | | MF | Mean | 11700000 | 65100 | 8.56 | 2060000000 | 444000000 | 2470000 | 445000 | 757 | 2.59 | 3.23 |
| | | | SD | 5380000 | 29900 | 12.0 | 966000000 | 216000000 | 1200000 | 405000 | 168 | 1.66 | 1.71 |
| | | | N | 9 | 9 | 9 | 4 | 9 | 9 | 4 | 4 | 9 | 9 |

NA Not applicable

Table excerpted from applicant's nonclinical package

Anti-Drug Antibody Analysis

Baseline anti-drug antibody (ADA) titers levels were ≤ 10 (lower limit of detection) in all 10 for monkeys administered the vehicle control article (0 mg/kg) at every sampling point, except for sample/titer of 50 in one male (# I10642) on the last day of recovery (Day 232). Sutimlimab was not detected in control samples at any time point. Sutimlimab was minimally immunogenic. ADA titers ≥ 50 were observed on more than one occasion (first observed on Day 57) in two out of ten monkeys administered 60 mg/kg/dose (# I10644, male and # I10658, female) and one out of ten monkeys administered 180 mg/kg/dose (# I10665, female). In these three monkeys, ADA titers were elevated prior to weekly dosing (e.g., 6250) but decreased 5 minutes after dosing (e.g., 1250) which is consistent with the binding of serum ADA to sutimlimab. ADA levels returned to ≤ 10 during recovery. Due to ADA formation, these three animals were excluded from toxicokinetic analysis. The increase in serum ADA in these three animals did not adversely affect the pharmacodynamic activity (classical complement inhibition) or adversely impact the health of animals (immune complex deposition) in these animals. Therefore, these infrequent instances of ADA did not affect the toxicological interpretation of the study.

Complement Analysis

Methods:

Sample aliquots of complement preserved pooled cynomolgus monkey serum (representing 100% activity) and heat-activated, complement-depleted, pooled cynomolgus monkey serum (representing 0% activity), were used as positive and negative controls. A standard curve was generated with complement-preserved pooled

cynomolgus monkey serum with concentrations of sutimlimab to provide intermediate levels of classical complement pathway (CCP) activity, up to and including no quantifiable (0%) CCP activity. The standard curve was also used to calculate the concentration of sutimlimab at which 50% CCP activity remains and 50% inhibition of the original CCP activity is observed (IC₅₀). CCP activity values for test serum samples were calculated from the positive and negative results. The reported values for monkey serum CCP activity were expressed as percent (%) “normal” monkey serum CCP activity.

Results:

The inherent serum complement activity was highly variable for individual animals in the treated groups. The baseline (pre-dosing) serum complement activity in the treated groups ranged from 78% to 140% compared to the complement preserved pooled cynomolgus monkey serum which represented 100% activity (positive control). There was no inhibitory activity in any control monkeys (0 mg/kg/dose) at any time point. Mean serum complement activity in the control group was 105% prior to dosing and remained $\geq 94\%$ at all time points. Sutimlimab, at 60 and 180 mg/kg/week caused a near complete inhibition (up to 98%) of classical complement activity, 5 minutes after injection and this inhibition persisted for 48 hours (Figure 7). This pattern was observed at every evaluation time point throughout the dosing period (up to day 176), (Figure 7). The degree of complement inhibition was not dose-dependent, thus indicating saturation of target at the lower dose. The pre-dosing classical complement activity was lower in the high dose group compared to the lower dose at every evaluation time point throughout the dosing period indicating prolonged complement inhibition at the higher dose (Figure 7). Also, a return to baseline classical complement activity occurred sooner at 60 mg/kg/week (Day 197) compared to 180 mg/kg/week (Day 232), (Figure 7). At 180 mg/kg/week, significant inhibition of serum complement activity was maintained for up to 31 weeks (thorough Day 211). The dose-response (complement inhibition) relationship exhibited a steep curve with an IC₉₀ value around 22 $\mu\text{g/ml}$ (Figure 8). Maximum/near complete inhibition of complement activity occurred at $>22 \mu\text{g/ml}$, while below this concentration essentially no complement inhibition was observed.

Figure 7. Mean Complement Activity in Monkeys Receiving 0, 60, or 180 mg/kg Sutimlimab IV Once Weekly for 26 Weeks

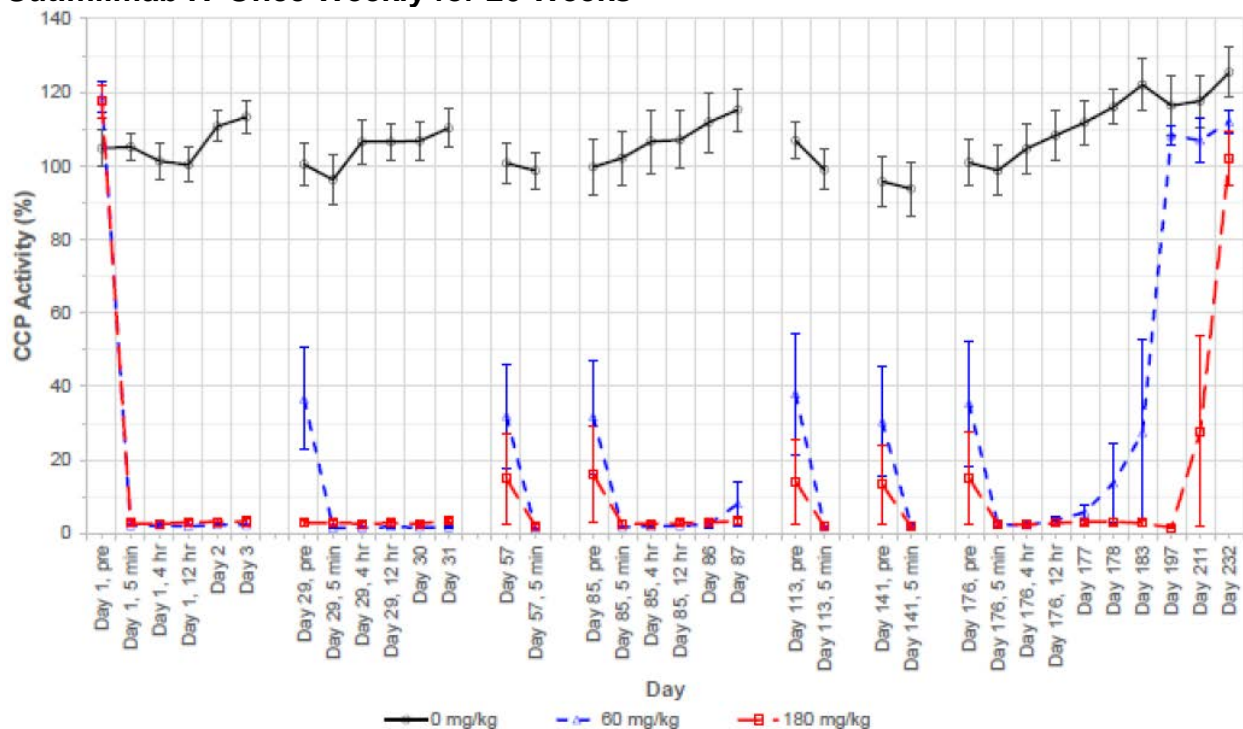


Figure excerpted from applicant's report

Figure 8. PD Relationship between Serum Sutimlimab Concentrations and CP Activity

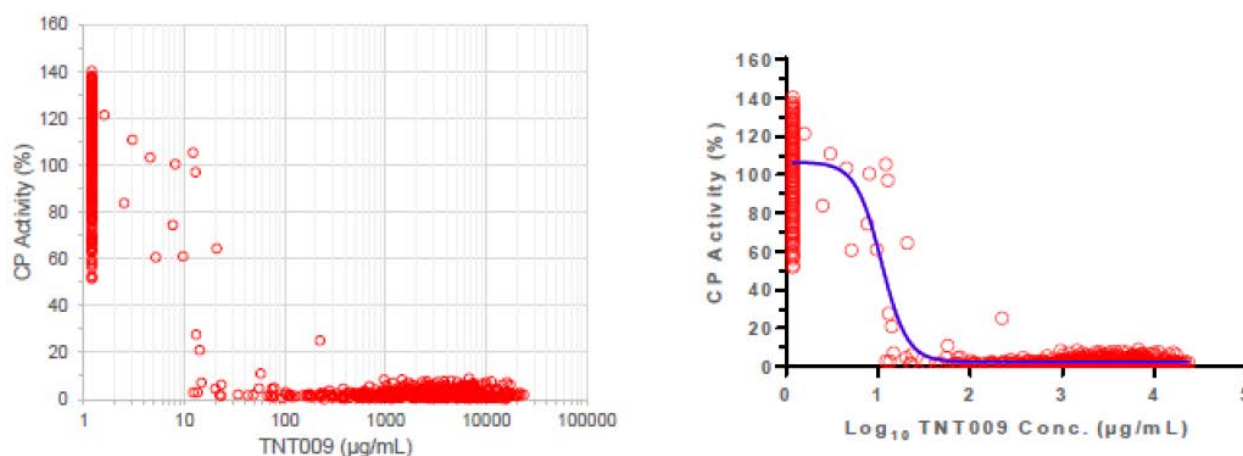


Figure excerpted from applicant's report

The NOAEL was 180 mg/kg weekly in male and female monkeys. The C_{max} attained in monkeys at NOAEL is 14 900/7800 µg/mL male/female which is much greater than the IC_{50} (14.7 µg/mL) for C1s inhibition in humans. Exposure in monkeys (AUC and C_{max}) indicate that the classical complement pathway is likely to be

completely inhibited at the NOAEL and thus can be considered an adequate toxicological evaluation of sutimlimab exposure in humans.

7 Genetic Toxicology

Sutimlimab is a large molecular weight monoclonal antibody (145 kDa). Genotoxicity testing is not relevant for this application.

8 Carcinogenicity

The applicant provided a weight-of-evidence (WOE) assessment to address the carcinogenic potential for sutimlimab. In brief, the applicant concluded that sutimlimab is highly unlikely to possess carcinogenic potential because: 1) a literature review did not identify published papers linking inhibition of C1s to carcinogenic risk; 2) long-term sutimlimab administration did not cause sutimlimab-related preneoplastic lesions in monkeys, the only pharmacologically relevant species tested; and, 3) tissue cross-reactivity studies demonstrated localization of sutimlimab in the vascular lumen and extracellular matrix, consistent with the ubiquitous presence of C1s in a soluble state in the plasma and extracellular fluid prior to activation.

An independent literature review indicated the applicant's literature assessment was appropriately conducted (see Appendix 1 for a detailed review of WOE). This reviewer did not find published evidence linking inhibition of C1s or the classical complement pathway to increased risk of carcinogenesis. Furthermore, the nonclinical studies conducted with sutimlimab did not indicate carcinogenic risk. Sutimlimab did not show significant binding to cellular structures or subcellular locations. Therefore, it is unlikely that sutimlimab possesses significant potential for carcinogenic risk. In addition, there are FDA-approved broad-spectrum complement inhibitors such as Berinert®, Cinryze®, and Ruconest® for which no carcinogenicity studies were conducted and there were no non-clinical findings indicative of carcinogenic potential up to the highest doses tested. These drugs are broad-spectrum inhibitors of multiple cascade pathways, including the complement system, coagulation cascade and fibrinolytic system, which is unlike sutimlimab, a specific C1s inhibitor that alters only the classical component. The selectivity of sutimlimab for classical component suggests a lesser likelihood for carcinogenic potential compared to the above marketed complement inhibitors.

CDER's Executive Carcinogenicity Assessment Committee's (ECAC) concurred with the reviewer's assessment. Thus, further characterization of the carcinogenic potential for sutimlimab is not warranted at this time.

9 Reproductive and Developmental Toxicology

9.1 Enhanced Prenatal and Postnatal Development Toxicity Study

Study title: Enhanced Pre- and Postnatal Developmental Toxicity

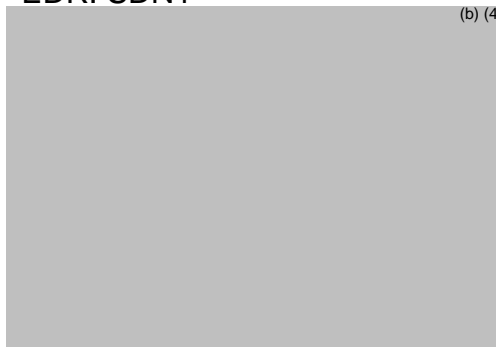
Study with BIVV009 in Cynomolgus Monkeys

Study no.: 8365131

Study report location: EDR: SDN1

Conducting laboratory and location:

Location for Statistical Evaluation of
Maternal Data:



Date of study initiation: August 10, 2017

GLP compliance: Yes, according to US-FDA GLP, CFR 21, part 58. Statistical evaluation was performed in accordance with UK GLP and OECD GLP.

QA statement: Signed QA statement included.

Drug, lot #, and % purity: Drug, TNT009 (BIVV009); Lot# 0000434249; Purity, 96.6%

Key Study Findings

Methods

| | |
|--------------------------|---|
| Doses: | 0, 60, 180 mg/kg/week |
| Frequency of dosing: | Once weekly, starting from GD20 till delivery (total 21 injections) |
| Dose volume: | 10 mL/kg for control and high dose; 3.3 mL/kg for low dose. Dose concentration was 18 mg/mL for low and high doses. |
| Route of administration: | Intravenous infusion |
| Formulation/Vehicle: | 10 mM phosphate, 140 mM sodium chloride, and 0.02% w/v polysorbate-80, pH 6.1 |
| Species/Strain: | Monkey/Cynomolgus |
| Number/Sex/Group: | 16 females/group |
| Satellite groups: | None |
| Study design: | Adequate. Infants were evaluated from birth up to 3 months of age. Low dose of 60 mg/kg was selected to provide a clinically relevant dose. High dose 180 mg/kg, the maximum feasible dose limited due to infusion volume limitation. A group size of 16 females/group was used to achieve at least 6 to 7 surviving infants on day-7 post-partum (per ICH S6). |

Key Findings:

- Sutimlimab was well tolerated in maternal animals and infants with no adverse effects observed at 180 mg/kg/week.
- Exposure to sutimlimab increased dose-dependently. Generally, there were no marked increases in anti-drug antibody levels at either dose. One animal in the low dose (60 mg/kg/week) had marked anti-drug antibody level with a correlating decrease in drug exposure. This animal was excluded from toxicokinetic analysis.
- There were no sutimlimab-related increases in markers of autoimmunity in the maternal monkeys or infants at any dose level compared to controls.
- Sutimlimab caused a marked non-dose-dependent decrease in serum complement pathway activity at ≥ 60 mg/kg/week.
- There were no sutimlimab-related adverse changes in maternal or fetal body weight, pregnancy, infant physical development and neurobehavioral parameters.
- NOAEL for the enhanced pre and post-natal developmental toxicity study is the high dose of 180 mg/kg/week due to the absence of sutimlimab-related adverse effects up to that dose.

Observations and Results

F₀ Dams

Mortality:

No sutimlimab-related mortality was observed.

Clinical Signs:

There were no sutimlimab-related adverse clinical symptoms in maternal animals post-coitum or post-partum. One monkey in the high dose group (180 mg/kg/week) had a hypersensitivity reaction on gestation day 111 and required veterinary treatment with diphenhydramine and ondansetron. The animal remained in the study and was administered sutimlimab as per schedule. Diphenhydramine was given to this animal before administering sutimlimab. The animal did not have further infusion-related reactions and delivered a healthy infant without incident.

Body Weight:

There were no sutimlimab-related changes in body weight or body weight gain in maternal animals during gestation or lactation phases.

Toxicokinetics:

Sutimlimab was administered via intravenous infusion at 60 and 180 mg/kg/week beginning on day 20 of gestation (post coitum day 20) till delivery. Serum BIV009 levels were measured on day 20, day 48, and day 146 of gestation. Mean drug concentrations increased with increasing dose in a dose-proportional manner (Table 10). The drug concentrations were below the limit of quantitation (LOQ) for the assay on post-partum day 28 for the 60 mg/kg/week group but were measurable in 5/14 animals in the 180 mg/kg/week group. Sutimlimab concentrations in the maternal milk and infant serum were below LOQ on day 28 post-partum.

Table 10. Mean sutimlimab Toxicokinetic Parameters in Maternal Monkey Serum following Once Weekly IV Infusion Administration During Gestation

| Interval (p.c. Day) | Dose Group | Dose Level (mg/kg/week) | C _{max} (µg/mL) | T _{max} (h) | AUC _{0-48.5} (h*µg/mL) | AUC ₀₋₁₆₈ (h*µg/mL) |
|------------------------|------------|----------------------------|-----------------------------|-------------------------|------------------------------------|-----------------------------------|
| 20 | 2 | 60 | 1540 | 0.583 | 40000 | NA |
| | 3 | 180 | 4100 | 2.54 | 118000 | NA |
| 48 | 2 | 60 | 1480 | 4.50 | 47300 | 96300 |
| | 3 | 180 | 7440 | 0.583 | 239000 | 620000 |
| 146 | 2 | 60 | 2020 | 2.59 | 61500 | 154000 |
| | 3 | 180 | 8110 | 4.50 | 313000 | 835000 |

Abbreviations: AUC: area under the concentration curve; C_{max}: maximum serum concentration; NA: not applicable; p.c.: post coitum; T_{max}: time of maximum concentration

Notes: Median values are presented for T_{max}.

Values are rounded to 3 significant figures.

Table excerpted from applicant's nonclinical package

Anti-Drug Antibody Analysis:

Compared to controls, marked anti-drug antibody (ADA) responses were infrequent in maternal animals and absent in infant animals in the 60 or 180 mg/kg/week group. The ADA titers were generally below 50 in the treated and control groups. Three maternal animals at 60 mg/kg/week (P0102, P0103 and P0106) and one animal at 180 mg/kg/week (P0209) had higher ADA titers (250 to 31300). Of these, P0106 exhibited markedly reduced (~20-fold) exposure to sutimlimab and was excluded from TK analysis starting on gestation day 46. None of the other animals (maternal and infant) showed reduced exposure to sutimlimab irrespective of the titer of ADA.

Autoimmunity:

The effect of sutimlimab on markers of autoimmunity (circulating immune complex-C1q, (CIC-C1Q), anti-extruded nuclear antigen immunoglobulin-G (anti-ENA IgG) antibody, and anti-double-stranded DNA IgG (anti-dsDNA IgG) antibody) were evaluated in maternal monkeys administered vehicle, 60 or 180 mg/kg/week during organogenesis and post-partum. Autoimmunity markers were also evaluated in the infant monkeys in the treated and control groups. There were no sutimlimab-related increases in markers of autoimmunity in the maternal monkeys (including animal P0209 that had one incident of hypersensitivity to infusion) or infants in the treated groups at any dose level compared to controls.

Classical Complement Pathway Inhibition:

Inhibition of the classical complement pathway (CCP) by sutimlimab was evaluated in monkeys administered vehicle, 60 or 180 mg/kg/week sutimlimab and in infants in their respective groups. Serum CCP activity was variable in individual monkeys ranging from 70% to 182%. No significant change in serum CCP activity was observed in control animals (serum CCP activity $\geq 111\%$ throughout dosing period). At ≥ 60 mg/kg/week, sutimlimab caused a marked non-dose-dependent decrease in serum CCP activity (CCP activity of 8%) starting at 5 minutes post-dose on day 1 of dosing, and $\leq 17\%$ at day 3 and staying at around 16% at day 146 (Table 11). The serum CCP activity returned to baseline levels by day 28 post-partum. There were no recorded instances of sutimlimab-related inhibition of CCP activity in infants in the treated groups compared to controls (136% in treated vs 121% in control) as measured in 28-day old monkeys, but CCP inhibition may have occurred in infants of sutimlimab-exposed mothers earlier during the post-partum period.

Table 11. Effect of Sutimlimab on Serum Complement Pathway Activity in Maternal Monkeys.

| | 0 mg/kg | 60 mg/kg | 180 mg/kg |
|----------------------|--------------|--------------|--------------|
| Day 20 p.c. Predose | 126.3 (14.9) | 126.9 (32.3) | 128.6 (25.3) |
| Day 20 p.c. 5 min | 124.3 (15.4) | 10.3 (9.8) | 8.3 (4.8) |
| Day 20 p.c. 4 hr | 133.4 (15.3) | 10.7 (9.8) | 10 (6.1) |
| Day 20 p.c. 8 hr | 136.8 (14.7) | 11.2 (8.3) | 14.1 (12.8) |
| Day 20 p.c. 24 hr | 139.6 (12.2) | 11.6 (11.7) | 12.9 (7.5) |
| Day 20 p.c. 48 hr | 144.9 (15) | 11.2 (8.3) | 17 (9.3) |
| Day 48 p.c. Predose | 126.8 (35.2) | 53.1 (67.1) | 14.3 (11.8) |
| Day 48 p.c. 5 min | 113.3 (50.2) | 7.2 (4) | 13.5 (9.2) |
| Day 48 p.c. 4 hr | 132.3 (42.4) | 8 (4.8) | 16.1 (10.8) |
| Day 48 p.c. 8 hr | 138 (33.2) | 8.2 (7.4) | 16.1 (12.3) |
| Day 48 p.c. 24 hr | 130 (48.6) | 9 (10.5) | 18 (14.7) |
| Day 48 p.c. 48 hr | 129.9 (40.1) | 7.7 (5.4) | 15.5 (9.9) |
| Day 146 p.c. Predose | 114 (41.5) | 23.9 (38.7) | 16.5 (32.1) |
| Day 146 p.c. 5 min | 116.1 (27.4) | 4.5 (2.2) | 9.8 (10.2) |
| Day 146 p.c. 4 hr | 126.5 (25.8) | 6.5 (5.2) | 11.3 (10.8) |
| Day 146 p.c. 8 hr | 131.3 (20.7) | 5.7 (4.3) | 11.3 (9.7) |
| Day 146 p.c. 24 hr | 127 (27.5) | 11.8 (16.3) | 9.3 (8) |
| Day 146 p.c. 48 hr | 128.2 (23.4) | 14.9 (29.7) | 8.8 (7.2) |
| Day 28 p.p. | 134.1 (29.6) | 131.5 (31.2) | 121 (50.7) |
| Day 42 p.p. | 128.9 (37.7) | 133.6 (30.1) | 144.6 (33) |
| Day 56 p.p. | 128.6 (39.0) | 119.9 (29.2) | 124.8 (12.2) |
| Day 70 p.p. | 118.8 (18.1) | 123 (23.8) | 137.7 (15.9) |
| Day 91 p.p. | 111.3 (19.4) | 100.3 (22.2) | 117.5 (11) |

Abbreviations: p.c.: post coitum; p.p.: post partum; SD: standard deviation

Table excerpted from applicant's nonclinical package

Pregnancy:

There were no sutimlimab-related effects on length of gestation or incidence of abortion in any of the treated-groups when compared to controls (Table 12). Pregnancy loss (abortion and stillbirths), which are fairly common in cynomolgus monkeys, was observed in all groups, including the control group. The incidence was within historical control range and was not dose-dependent and therefore was not considered related to sutimlimab.

Table 12. Summary of Pregnancy Outcome - Incidence of Abortions, Stillbirths, and Early Infant Deaths

| During Gestation | Group 1 0 mg/kg/dose No. (%) | Group 2 60 mg/kg/dose No. (%) | Group 3 180 mg/kg/dose No. (%) |
|---|------------------------------------|---|--------------------------------------|
| Total number of pregnant females | 16 | 16 | 16 |
| Mean length of gestation (days) | 165 | 162 | 162 |
| Females with abortion | | | |
| - 1 st Trimester Abortions (GD0-50) | 1 (6) GD40 | 3 (19) GD26, 33, 40 | 1 (6) GD33 |
| - 2 nd Trimester Abortions (GD51-100) | 0 | 0 | 0 |
| - 3 rd Trimester Abortions (GD101-144) | 0 | 0 | 1 (6) GD139 |
| Total number of stillbirths | 0 | 2 (13) GD168 ^a , 176 | 0 |
| Total number of abortions and stillbirths | 1 (6) | 5 (31) | 2 (13) |
| Total number delivered | 15 (94) | 13 (81) | 15 (94) |
| - Total number of early infant deaths | 0 | 0 | 0 |
| - Total number of infants euthanatized | 1 (6) PND70 ^b | 2 (13) PND1 ^c , 58 ^b | 0 |
| - Total number of surviving infants | 14 (88) | 9 (56) | 14 (88) |

a No heartbeat noted by ultrasound, infant delivered stillborn by c-section at time of maternal necropsy

b Infant sacrificed due to injury

c Infant sacrificed due to maternal rejection

Table excerpted from applicant's nonclinical package

Clinical Chemistry and Hematology:

The only clinical chemistry/hematology change attributable to sutimlimab was a minimal (17%) increase in serum globulin at 180 mg/kg/week (high dose) compared to control values (Table 13). Increased serum globulin resulted in a corresponding 22% decrease in albumin/globulin ratio at 180 mg/kg/week. There were no correlating changes in markers of inflammation, metabolism, or macroscopic and microscopic changes at 180 mg/kg/week. This minimal change in globulin is likely related to increased (IgG) drug concentrations and is not likely to represent a toxicological concern.

Table 13. Summary of Globulin Levels in Sutimlimab-Treated Maternal Animals

| ALB (g/dL) | GLOB (g/dL) | A:G (Ratio) |
|---------------|----------------|----------------|
| 12 | 12 | 12 |
| 3.1 | 3.5 | 0.9 |
| 0.32 | 0.43 | 0.13 |
| 12 | 12 | 12 |
| 2.9 | 3.7 | 0.8 |
| 0.26 | 0.44 | 0.14 |
| 11 | 11 | 11 |
| 2.8 | 4.1+H | 0.7+H |
| 0.32 | 0.40 | 0.11 |

Table excerpted from applicant's report

Pathology:

There were no sutimlimab-related macroscopic or microscopic changes at any dose level.

F₁ Generation

Survival:

There was no sutimlimab-related mortality in infants at any dose level. Infant mortality, unrelated to sutimlimab (trauma, still birth), was observed in all groups including controls (Table 14).

Table 14. Summary of Infant Mortality in the E-PPND Study

| Animal Number | Sex | Dose Group | Day | Remarks |
|---------------|-----|------------|---------|--|
| P0007-1 | F | 1 | PND 70 | Trauma |
| P0109-1 | M | 2 | PND 1 | Maternal rejection |
| P0115-1 | M | 2 | GD 168 | No heartbeat noted by ultrasound, delivered by c-section |
| P0104-1 | F | 2 | PND 176 | |
| P0110-1 | F | 2 | PND 58 | Trauma |

GD = Gestation day; PND = Postnatal day.

Table excerpted from applicant's nonclinical package

Clinical Signs:

There were no sutimlimab-related adverse clinical signs in infants at any dose level.

Body Weight:

There were no sutimlimab-related changes in body weight at any dose level compared to controls.

Physical Development:

No sutimlimab-related adverse effects were observed for physical development, grip strength, and organ weights at any dose level compared to controls.

Neurobehavioral Assessment:

There were no sutimlimab-related adverse neurobehavioral effects at any dose level compared to controls.

Macroscopic and Microscopic Observations:

There were no sutimlimab-related macroscopic or microscopic pathology at any dose level compared to controls.

10 Special Toxicology Studies

10.1 TN-1406: Assessment of Potential Cross Reactivity of TNT009 with a Selected Panel of Human Tissues

Method:

The potential for cross-reactivity of sutimlimab (TNT009) on human tissues was evaluated using an immunohistochemical (IHC) visualization of sutimlimab binding to a select panel of human tissues from three donors (Table 10). Cryosectioned, 5 µm-thick human tissues were incubated with biotinylated sutimlimab IgG4 and visualized using horse-radish peroxidase and diaminobenzidine. Biotinylated human IgG4 was used as isotype control. The study was compliant with the “Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use” published in February 1997 by the FDA and the “Guideline on Development, Production, Characterisation and Specifications for Monoclonal Antibodies and Related Products” (EMA/CHMP/BWP/157653/2007) published in December 2008 by the EMA. Tissue viability was demonstrated by positive staining for vimentin, cytokeratin, and von-Willebrand Factor. Human bladder tissue and human liver tissue (obtained from (b) (4)) were used as positive control material for sutimlimab IHC staining. The IHC staining was graded on a scale of 1 to 5 to demonstrate intensity of specific sutimlimab staining.

Results:

Specific positive staining for sutimlimab was observed in most tissues examined with staining predominantly localized on blood vessel walls and connective tissue. In blood vessels, specific positive staining was observed predominantly within the tunica media, tunica adventitia, endothelium and within the lumen of the vessel. In the connective tissue, specific positive staining was generally observed within the fibrovascular and fibromuscular tissue. Staining was observed to be ubiquitous in endodermal and mesodermal derived tissues and present in the lumen of blood vessels or extracellular matrix and not on cell surfaces. There was positive staining within some smooth muscle and skeletal muscle cells in the cytoplasm which is of no toxicological significance due to inability of access for the antibody to intracellular compartments. The staining is confined to blood vessel lumen or extracellular matrix and not bound to cellular structures. Furthermore, the widespread nature of sutimlimab staining observed in human tissues is to be expected given the ubiquitous distribution of the C1s protein (antigen for the sutimlimab antibody) and does not present any toxicological concern.

9.2 EpiScreen™ Time Course Assay of Fully Humanized Antibody**Method:**

The purpose of the study was to evaluate the immunogenic potential of the full C1s monoclonal antibody (sutimlimab) when compared against the reference chimeric antibody. Keyhole limpet haemocyanin (KLH) a known inducer of T-cell proliferation was used as positive control. Peripheral blood mononuclear cells (PBMC) were collected from 20 donors to best represent the number and frequency of HLA-DR expressed in the world population. CD8+ T cells from PBMC were depleted. The immunogenicity potential of sutimlimab was determined by measuring the ex vivo T cell responses against sutimlimab when compared to the chimeric antibody using the EpiScreen™ time course T cell assay. PBMC were incubated with 50 µg/mL sutimlimab or chimeric antibody or with 100 µg/mL KLH (positive control) for 8 days at 37°C with 5% CO₂. On days 5,6,7, and 8, the cells were pulsed with 0.75 µCi [3H]-Thymidine and incubated for a further 18 hours. Counts per minute (cpm) for each group were determined using a scintillation counter. Samples showing a stimulation index (SI) ≥2 were considered positive for proliferation.

Results:

- The chimeric antibody had significant potential for immunogenicity (45% proliferation potential) while sutimlimab treated groups did not show proliferation of T-cells (0% donor response rate, see Table 15 below).
- Positive control (KLH)-treated groups showed a 95% donor response (T-cell proliferation).

From the results above, it appears that sutimlimab does not possess a potential to stimulate proliferation of T-cells (lacks immunogenicity).

Table 15. Summary of T-cell Proliferative Responses

| | IPI03 VH4/Vk2 | IPI03 chimeric | KLH |
|-----------------|------------------|-------------------|-----|
| Donor 1 | | P | P |
| Donor 2 | | P | P |
| Donor 3 | | P | P |
| Donor 4 | | P | P |
| Donor 5 | | P | P |
| Donor 6 | | P | P |
| Donor 7 | | | P |
| Donor 8 | | P | P |
| Donor 9 | | | P |
| Donor 10 | | | P |
| Donor 11 | | | P |
| Donor 12 | | P | P |
| Donor 13 | | P | |
| Donor 14 | | | P |
| Donor 15 | | | P |
| Donor 16 | | | P |
| Donor 17 | | | P |
| Donor 18 | | | P |
| Donor 19 | | | P |
| Donor 20 | | | P |
| Proliferation % | 0 | 45 | 95 |

Table 1: Summary of healthy donor T cell proliferation responses. Positive T cell responses (SI \geq 2.00, significant $p < 0.05$) ("P") and borderline T cell responses (significant $p < 0.05$ with SI \geq 1.90) ("P*") for proliferation during the entire time course days 5-8 are shown. The frequency of positive T cell responses for proliferation are shown as a percentage at the bottom of the columns. No day 7 data was obtained from donor 19.

Table excerpted from applicant's report

10 Integrated Summary and Safety Evaluation

Bioverativ USA Inc. seeks to market sutimlimab (BIVV009, TNT009), a first-in-class humanized IgG4 monoclonal antibody against complement C1s for the treatment of hemolysis in adult patients with cold agglutinin disease (CAD). Sutimlimab inhibits the complement 1s (C1s) component of the classical complement pathway. As this antibody does not inhibit the lectin and alternate complement pathways, complement-mediated immune surveillance is not likely to be totally abrogated. Pharmacological proof-of-efficacy was demonstrated in vitro in human and cynomolgus monkey serum. In vitro, sutimlimab displayed high affinity binding (2.6×10^{-10} M) and potent and complete inhibitory activity ($IC_{50} = 1.9 \times 10^{-9}$ M) on human C1s of the classical component pathway while not altering the activity of alternate and lectin complement pathways. Cynomolgus monkey was the only pharmacologically relevant non-human species identified. Sutimlimab displayed comparable binding to human and monkey C1s (1.5×10^{-10} M and 1.3×10^{-10} M, respectively) and comparable inhibition of classical complement-mediated hemolysis in 20% human and monkey serum ($IC_{50} = 5.1$ and 4.1 μ g/mL, respectively).

In both humans and monkeys, sutimlimab exhibits linear elimination kinetics at low dose and non-linear elimination kinetics at high dose. The half-life is increased, and clearance is decreased as the dose is increased. In humans the half-life of sutimlimab was ~ 21 days, which is typical for IgG. Interestingly, the half-life of sutimlimab in monkeys was uncharacteristically short (~100 hours). While the reasons for the short half-life observed in monkeys is unknown, it could indicate target-mediated clearance. The short half-life in monkeys was accounted for in the study design for repeat-dose studies in which sutimlimab is administered weekly, while in humans the drug will be administered every other week. Drug exposure and pharmacodynamic activity was confirmed in all monkeys throughout the 26-week toxicity study.

Secondary pharmacology studies were not conducted for sutimlimab. A tissue cross reactivity study using a select panel of 40 tissues from three human donors demonstrated no unexpected specific staining for sutimlimab in cellular structures. Sutimlimab staining was confined to blood vessel lumen or extracellular matrix. The widespread nature of sutimlimab staining observed in human tissues is to be expected given the ubiquitous distribution of the C1s protein (antigen for sutimlimab) and does not suggest any toxicological concern. Furthermore, sutimlimab selectively inhibits the C1s component of the classical complement pathway leaving lectin and alternate arms of the complement system intact. No potential for off-target toxicity was identified.

Safety pharmacology endpoints were included in the repeat-dose toxicology studies in cynomolgus monkeys. Cardiovascular and respiratory function testing included heart rate monitoring, body temperature, oxygen saturation, ECG testing and evaluation of respiration, which were unremarkable at doses up to 180 mg/kg weekly for 26 weeks (exposure based on AUC was approximately 3- or 5-fold greater than that at 6.5 g or 7.5 g clinical dose). There was no indication of central nervous system (CNS) effects or effects on neurobehavioral endpoints in monkeys at doses up to 180 mg/kg weekly for 26 weeks.

A pivotal GLP-compliant 26-week intravenous repeat-dose toxicology study was conducted in nonhuman primates, the only pharmacologically relevant species identified. In this study, sutimlimab was administered over a 30-minute infusion to 2 dose groups (60 and 180 mg/kg), once weekly, for 26 consecutive weeks with an 8-week recovery period. Sutimlimab was tolerated up to the highest dose of 180 mg/kg (exposure approximately 3- or 5-fold greater than that at 6.5 g or 7.5 g clinical dose, based on AUC) with no adverse effects on the health of the animals. No adverse macroscopic or microscopic changes were observed up to the highest dose tested (180 mg/kg/week). There was no C1s inhibition-related increase in infection at either dose; however, it should be noted that these studies are conducted in healthy monkeys housed in controlled environments without exposure to pathogens, and potential exacerbation of infection by C1s inhibition therefore remains a theoretical risk of sutimlimab. At the end of the study, sutimlimab showed a nearly 20-fold increase in exposure at 180 mg/kg/week (AUC, 2060 mg/ml) compared to 60 mg/kg/week (AUC, 108 mg/ml), which was greater than expected based on a 3-fold higher dose. The

greater-than-dose-proportional-increase observed is consistent with the findings from a separate 5-week repeat-dose pharmacokinetic study in monkeys, which showed decreasing clearance and increasing half-life at the high dose of 100 mg/kg/week compared to the low dose of 30 mg/kg/week. There were no significant differences in systemic exposures (C_{max} and AUC) between males and females.

Sutimlimab was minimally immunogenic in monkeys (most anti-drug antibody titers were ≤ 10). However, there were sporadic cases of increases in anti-drug antibody titer (≥ 50) in two monkeys administered 60 mg/kg/dose (# I10644, male and # I10658, female) and in one monkey administered 180 mg/kg/dose (# I10665, female), first observed on Day 57. In these three monkeys, ADA titers were elevated prior to weekly dosing and subsequently reduced at 5 minutes after dosing, consistent with the binding of serum ADA to the IV-administered sutimlimab. ADA returned to titer levels of ≤ 10 in all recovery animals. The increase in serum ADA in these three animals did not affect the magnitude of sutimlimab-mediated inhibition of complement activity; however, duration of complement inhibition was shortened, due to faster clearance, indicated by a return to baseline activity before dosing in these animals. A T-cell proliferation assay using peripheral blood mononuclear cells isolated from 20 donors with varied HLA-DR allotypes was negative. It should be noted that genetic deficiency of early components of the classical complement pathway (C1q, C1r-C1s) is associated with development of autoimmune disease⁵. It is unclear if inhibition of C1s by sutimlimab would present a risk of autoimmunity because C1q is thought to inhibit autoimmune response through complement independent mechanisms⁶. Although pharmacological inhibition of C1s is fundamentally different from genetic deficiency of C1s, since autoimmune diseases are associated with severe morbidity, the Agency communicated to the sponsor (late cycle meeting, September 21, 2020) that long term risk of autoimmunity remained a concern and should be monitored.

In repeat-dose toxicity studies in monkeys, sutimlimab caused a near-complete inhibition (up to 98%) of serum classical complement pathway activity, beginning on day 1, 5 minutes after injection of 60 and 180 mg/kg doses and persisting till the last evaluation time-point (48 hours) and remained inhibited when measured before dosing on day 29. The duration of inhibition was dose-dependent with maximum inhibition of 97% for high dose and 63% for low dose observed before start of dosing on day 29. Similar pattern of complement inhibition was observed through-out the remaining evaluation time points. Sutimlimab was detectable in both dose groups when analyzed before start of dosing at every time point. The degree of complement inhibition was not dose dependent, indicating saturation of target at the lower dose. The pre-dosing classical complement activity was lower in the high dose group compared to the lower dose at every evaluation time point throughout the dosing period indicating prolonged complement inhibition at the higher dose. Also, a return to baseline classical complement activity occurred sooner at 60 mg/kg/week (Day 197, 21 days after last

⁵ Macedo, AC, and Isaac, L, 2016, Systemic Lupus erythematosus and Deficiencies of early Components of the Complement Classical Pathway, *Front.Immunol*, 7:55

⁶ Son, M, Diamond, B, and Santiago-Schwarz, F, 2015, Fundamental Role of C1q in Autoimmunity and Inflammation, *Immunol Res*, 63(1-3):101-106.

dosing) compared to 180 mg/kg/week (Day 232, 56 days after last dosing). Therefore, the duration of inhibition appeared to be dose-dependent which is a typical pharmacokinetic/pharmacodynamic profile for mAb drugs, where low doses completely saturate target, but higher doses increase the duration of maximal pharmacodynamic effect due to prolonged clearance time.

The no observed adverse effect level (NOAEL) in the repeat-dose toxicity study was 180 mg/kg weekly in male and female monkeys. The mean C_{max} (M+F) attained in monkeys at NOAEL is 11350 µg/mL, which is much greater than the IC₅₀ (14.7 µg/mL) for C1s inhibition in humans. Exposure in monkeys (AUC and C_{max}) indicated that the classical complement pathway was likely to be completely inhibited throughout the dosing period at the NOAEL and thus the repeat-dose toxicity study can be considered an adequate toxicological evaluation of sutimlimab exposure in humans.

Sutimlimab has a molecular weight of 145 kDa. The large and complex structure of this antibody makes any entry into the nucleus and reaction with DNA unlikely. Also, no impurities or degradants of toxicological concern were observed for the drug product. Based on the above reasons, genotoxicity testing was not recommended for this application.

The applicant's non-clinical package did not include a traditional in vivo carcinogenicity assessment. Instead, the applicant provided a weight-of-evidence (WOE)-based assessment of carcinogenic potential (per ICH S6). The applicant, from their WOE based on literature review, long-term repeat-dose toxicity study in monkeys, and cross reactivity studies in human tissues concluded that sutimlimab was unlikely to possess carcinogenic potential. An independent literature review, as well as an evaluation of the applicant's WOE-based justification was conducted by the reviewer (see Appendix 1 for a detailed review of WOE). No published evidence linking inhibition of C1s or the classical complement pathway to increased risk of carcinogenesis was found. Furthermore, an evaluation of the carcinogenic potential of sutimlimab from applicant-submitted nonclinical studies concluded that it is unlikely that sutimlimab has significant potential for carcinogenic risk. The nonclinical safety profile of sutimlimab for carcinogenic potential is consistent with the lack of adverse effects at the high dose and absence of proliferative lesions observed with marketed broad-spectrum complement cascade inhibitors Berinert®, Ruconest® and Cinryze®. FDA's Executive Carcinogenicity Assessment Committee's (ECAC) concurred with this conclusion. Thus, no further assessment of carcinogenic potential for sutimlimab is recommended.

An enhanced pre- and post-natal developmental toxicity study was conducted in monkeys with 60 or 180 mg/kg/week of sutimlimab to evaluate embryo-fetal and post-natal developmental toxicity of sutimlimab. There were no sutimlimab-related adverse changes in maternal or fetal body weight, pregnancy, infant physical development and neurobehavioral parameters up to the 180 mg/kg/week, the NOAEL (exposure at NOAEL based on AUC is approximately 3 or 2-fold greater than that at 6.5g or 7.5g clinical dose, respectively). Sutimlimab caused the expected inhibition of classical complement pathway activity in maternal animals, but no complement inhibition was

observed in infants up to the highest dose (180 mg/kg/week) as first assessed on postnatal day 28 Serum classical complement activity returned to baseline levels in maternal animals by day 28 post-partum. This relatively quicker return to baseline may be due to the short half-life for this antibody (~24 hours at 60 mg/kg/week increasing to ~100 hours at 100 mg/kg/week, based on a separate PK study in monkeys).

In conclusion, sutimlimab demonstrated pharmacological activity relevant for the proposed indication in both in vitro and in vivo systems. Sutimlimab was well tolerated in a chronic monkey toxicology study, with an adequate safety profile after repeated administration of the drug (3- to 5-fold safety margin to human clinical exposure) and with no safety or efficacy concerns due to immunogenicity. Sutimlimab did not cause adverse reproductive outcomes with administration to pregnant monkeys at up to 4 times the clinical exposure at the 7.5g clinical dose. Sutimlimab is unlikely to possess significant carcinogenic risk. There are no nonclinical concerns that would preclude the marketing of sutimlimab.

12 Appendix/Attachments

Appendix 1

BLA 761164: Review of Applicant's Weight-of-Evidence-based Assessment of the Carcinogenicity Potential for Sutimlimab (Enjaymo®)

Background

The applicant, Bioverativ/Sanofi, proposes to market sutimlimab (Enjaymo), a first-in-class humanized IgG4 monoclonal antibody against complement C1s, for treatment of hemolysis associated with cold agglutinin disease (CAD). Hemolysis in CAD is an auto-immune phenomenon resulting from classical complement pathway-mediated destruction of RBCs due to auto-antibody (IgM). Sutimlimab specifically inhibits C1s serine protease, which cleaves the first soluble substrate (C4) of the classical complement pathway. The other two arms of the complement activation system, namely the alternative and lectin pathways, are not altered by sutimlimab, thus maintaining immune surveillance function of the complement system. This brief review presents the applicant's rationale for claiming limited carcinogenic potential of sutimlimab, followed by this reviewer's independent assessment and regulatory recommendation.

Applicant justification

Sutimlimab was granted breakthrough therapy designation for CAD on May 17, 2017 (under IND 128190) and the initial rolling BLA submission (containing non-clinical information) arrived on July 24, 2019. The applicant's non-clinical package did not include carcinogenicity studies. Instead, the applicant provided a weight-of-evidence (WOE) justification (per ICH S6) to address the carcinogenic potential for sutimlimab. In brief, the applicant concluded (refer also to the applicant's WOE assessment for

additional details) that sutimlimab does not possess carcinogenic potential based on the following:

1. A literature review did not identify published papers linking inhibition of C1s to carcinogenic risk.
2. The absence of preneoplastic lesions related to sutimlimab exposure in monkeys, the pharmacologically relevant species.
3. Tissue cross-reactivity studies demonstrated binding of sutimlimab to the expected cellular structures (e.g., vascular lumen and extracellular matrix), which is consistent with the expression of C1s but did not show significant binding in unexpected tissues or subcellular locations.

Reviewer assessment

An independent literature review did not find evidence linking inhibition of C1s or the classical complement pathway to increased risk of carcinogenesis. Whereas evidence linking activation of complement system in promoting⁷ or inhibiting neoplasia⁸, and evidence linking inhibition of complement system as a tool to inhibit tumor formation^{9 10} are available, there was no evidence linking specific C1s inhibition to tumor formation.

The monkey was the only pharmacologically active species and sutimlimab demonstrated comparable efficacy as compared to humans. Binding of sutimlimab to C1s was not detected in dogs, mini-pigs, rabbits, mice, or rats. In a chronic (26-week) toxicity study in monkeys, sutimlimab was administered by 30-minute infusion at 60 and 180 mg/kg, once weekly, with an 8-week recovery period. The study included assessments of antigenicity and inhibition of complement. Sutimlimab administration resulted in a dose-dependent increase in duration of inhibition of serum complement activity. Sutimlimab was well tolerated up to the highest dose in monkeys (180 mg/kg), which represents a 3 to 5-fold higher exposure than human exposures at the maximum human clinical dose of 6.5 to 7.5 grams. There were no adverse changes in organ weights or histopathological evidence of hyperplasia or neoplasia related to sutimlimab exposure at either dose. The C_{max} measured in monkeys at 180 mg/kg/week (14,900/7,800 µg/mL male/female) greatly exceeds the IC_{50} (14.7 µg/mL) for human C1s inhibition measured in vitro. Sutimlimab exposures, as measured by both AUC and C_{max} , suggest that classical complement pathway in monkeys was constantly inhibited to a high degree at the NOAEL dose. Therefore, I consider the chronic monkey study to be an adequate toxicological assessment of exposure for evaluation of human risk. Tissue cross reactivity studies using 40 human tissues from 3 donors did not reveal any specific staining of sutimlimab, except for in the lumen of blood vessels and extracellular matrix, which are the expected locations for C1S.

⁷ British Journal of Dermatology (2020) 182, pp658–670.

⁸ Front Immunol. 2018 Sep 25; 9:2203.

⁹ Semin Immunol. 2013 February; 25(1): 54–64.

¹⁰ Cancer Immunol Res. 2014 Mar;2(3):200-6.

There are U.S.-approved inhibitors of complement pathway marketed for other indications, including Berinert® (C1 esterase inhibitor, human), Cinryze® (C1 esterase inhibitor, human) and Ruconest® (C1 esterase inhibitor, recombinant) for hereditary angioedema and Soliris® (eculizumab) for paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. Berinert and Cinryze are naturally occurring C1 esterase inhibitors purified from plasma; Ruconest is a recombinant C1 esterase inhibitor. These drugs are broad-spectrum inhibitors of multiple cascade pathways, including the complement system, coagulation cascade and fibrinolytic system, which is unlike sutimlimab, a specific C1s inhibitor that alters only the classical component. Soliris is a humanized IgG2/4 monoclonal antibody that inhibits the terminal phase C5 component of the complement pathway that results in membrane attack complex. The labels for the above drugs indicate that no carcinogenicity studies were conducted. Indeed, there were no non-clinical findings indicative of carcinogenic potential up to the highest doses tested.

Regulatory recommendation

Based on the above, it is unlikely that sutimlimab has significant potential for carcinogenic risk. The applicant's weight-of-evidence justification is acceptable, and this reviewer does not recommend further assessment of carcinogenic potential for sutimlimab.

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/s/

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I concur